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10/617,067	07/10/2003	David G. Beer	UM-08196	8445

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EXAMINER	
SANG, HONG	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,067	BEER ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Beer et al.

1. Applicant's election without traverse of Group II (claims 1-7, detecting the presence of a polypeptide corresponding to the marker) and the marker GSTM4 in the reply filed on 2/2/07 is acknowledged.

2. Claims 1-7 are pending. Claims 8-14 are cancelled. Claim 3, drawn to detecting the presence of mRNA, is withdrawn from further consideration as being drawn to non-elected inventions.

3. The information disclosure statement (IDS) filed on 2/2/07 has been considered. A signed copy is attached hereto.

4. Claims 1, 2 and 4-7 are under examination.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code see page 77, line 13, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code found throughout the specification. See MPEP § 608.01.

6. The disclosure is objected to because of the following informality.

A. The Brief Description of the Drawings is objected for the following informality.

(i). The "Fig.4D" is mentioned in the description of Figure 3 (see page 6, line 29), however, Fig.4D is not found in the Drawings.

(ii). The terms "(3A)" and "(3B)" are mentioned in the description of Figure 11 (see page7, lines 30 and 31). It is unclear what these terms reference to.

(iii). The terms "Figure 12A", "Figure 12B" and "Figure 12C", which are cited in the description of Figure 12, should be changed to "Box A", "Box B" and "Box C", respectively.

B. The specification cites Tables 3, 4, and 5 (for example at pages 7, line 3, page 92, line 2, and page 92, line 24, respectively). However, No Tables 3, 4 and 5 are found in the specification.

Claim Objections

7. Claims 1, and 4-7 are objected to because of the following informalities: claims contain non-elected inventions, i.e. non-elected markers such as AOE372, ATP5D, etc. Furthermore, claim 1 encompasses detection of the mRNA of the markers. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 2 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting lung cancer in a

subject, comprising detecting the presence of GSTM4 polypeptide in lung tissue of said subject, does not reasonably provide enablement for a method for identifying a stage of lung cancer in a subject, a method for providing a prognosis of lung cancer in a subject comprising detecting the presence of GSTM polypeptide in lung tissue of said subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method for characterizing lung tissue in a subject comprising detecting a decreased or increased expression relative to non-cancerous lung tissue control of GSTM4 polypeptide, thereby characterizing said lung tissue sample, wherein said characterizing said lung tissue comprising identifying a stage of lung cancer in said lung tissue, and providing a prognosis to said subject.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v.

Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The term "providing a prognosis" means to provide information regarding the impact of the presence of cancer, e.g., expected morbidity or mortality, the likelihood of getting cancer, the risk of metastasis or recurrence, the likelihood of response to treatment. The term "characterizing the lung tissue" encompasses detecting lung cancer, identifying a stage of lung cancer and providing a prognosis of lung cancer.

Quantity of experimentation

The quantity of experimentation in this area is extremely large in view of the breadth of the claims.

The unpredictability of the art and the state of the prior art

Armstrong et al. (see Recent Results Cancer Res. 2005: 166:99-112) teach that finding a single surrogate marker that serves well across all populations and treatments seems unlikely and multiple studies across treatments and populations will be required to characterize the biomarker and demonstrate its characteristics as a surrogate endpoint, and the ultimate judgment of surrogate endpoint utility will vary by disease process and intervention, and the standards required for judgment will differ correspondingly (see page 102, last paragraph). Armstrong et al. teach that despite much work, to date no prehistologic biological or molecular intermediate marker has

been validated for sporadic cancers and the current strategies to develop biochemical and genetic markers to identify surrogate biomarkers is flawed, and need to be reassessed in light of the difficulties faced over the last 20 years (see abstract). Srinivas et al (Clinical Chemistry, 47(10), 1901-1911, 2001) teach that the cellular proteome is a dynamic profile and is subject to changes in response to various signals and as a part of disease progression and this occurs through a interplay of posttranslational modification, translocation, protein-protein interactions, and protein-nucleic acid interaction (see page 1908, left column, third paragraph). Srinivas et al. teach that given the complex nature of carcinogenesis and the heterogeneous nature of cellular interaction within the microenvironment of a tumor, analysis of appropriate cell population is necessary to obtain meaningful proteomic output and screen out background noise Srinivas et al also teach that as new protein biomarker are discovered through proteomic approaches, the necessity to validate and ultimately use them in a clinical setting increases (see page 1908, right column).

Thomas et al. (Curr. Opin. Pulmonary Med., 2004, 10: 242-247) teach that "proteomic analysis may yield biomarker information with good or better a degree of practical utility than those being identified by other methodologies. Issues that need to be addressed include the fact that protein peaks do not represent actual proteins and the determination of the specific protein represent in the peak remains difficult and timely. For potential biomarkers identified in all of the above mentioned high throughput technologies, significant questions remain in respect to their reproducibility and capacity

for practical application. Therefore, results from all these technologies must be reproduced in larger validational studies" (see page 243, right column 3rd paragraph).

Zhu et al. (J. Clin. Pathol., 2006:59:790-800) teach that of 17 prognosis markers for non-small cell lung caner that have been investigated by eight or more groups, none have shown consistent results in all studies (see page 794, right column, 3rd paragraph). Zhu et al. teach that studies on prognostic markers, particularly, but not exclusively those including immunohistochemical assays, often give rise to inconsistent or contradictory results (see page 794, last paragraph). Zhu et al. teach that correlations with stage or tumor grade may provide insight into the tumor biology, but are weak and inadequate parameters for assessing the significant of the outcome (see page 796, right column, 3rd paragraph). Zhu et al. teach that whereas an individual marker was not prognostic, a combination phenotype could be prognostic (see page 797, 1st paragraph).

Therefore, in view of the unpredictability of cancer prognosis, a cancer marker identified by proteomic analysis must be further validated before it can be use to predict the cancer outcome.

Working examples

The specification teaches proteomic analysis of lung adenocarcinomas, wherein 2D-PAGE, and the separated proteins were further identified by mass spectrometry, polypeptide sequencing or 2D western blotting (see Example 2). The specification teaches that by comparing protein expression levels between 93 lung adenocarcinomas

and 10 uninvolved lung samples, 9 different enzyme proteins were identified using 2D-PAGE and MALDI-MS or peptide sequencing (see page 91, lies 10-20). The specification teaches that GSTM4 polypeptide was detected in 96.8% of the lung tumors, and was increased 4 fold in lung adenocarcinomas as compared to normal lung tissue (see page 12, lines 15-20).

While the specification teaches a correlation between the survival and the gene expression profile, the survival data and stage classification were established on the analysis of the gene expression profile, not individual gene (see Figure 1, Figure 4, and page 75 last paragraph). The specification does not disclose that there is a correlation between the expression level of GSTM4 polypeptide and the stage of a lung cancer, or the likelihood outcome of the lung cancer. Given the teaching of the specification that no correlation was found between expression of GSTM4 polypeptide and that of GSTM4 mRNA (see page 92, lines 25-27), one skilled in the art would not be able to predict the prognostic ability of the GSTM4 polypeptide.

Furthermore, claim 1 part b) recites detecting a decreased or increased expression relative to a non-cancerous lung tissue control of the marker GSTM4. The specification teaches that the GSTM4 mRNA is over expressed in lung cancer tissue. As such, a method of characterizing lung tissue by detecting a decreased expression of GSTM4 polypeptide is not enabled.

Guidance in the specification

The specification provides insufficient guidance and objective evidence to

indicate to one of skill in the art that the expression level of GSTM4 polypeptide is capable of predicting the outcome of lung cancer.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example that does not address the correlation between the expression level of GSTM4 polypeptide and lung cancer prognosis and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 2, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cantlay et al. (Thorax, 1994, 49:1010-1014).

Cantlay et al. teach immnohistochemical detection of GSTM1 polypeptide in lung tissues obtained from 21 human subjects having lung cancer using polyclonal antibody for GSTM1, wherein two cases of the 21 showed strong staining, seven were weekly stained and the remainder were negative (see page 1011, 1st paragraph, and page 1013, 2nd paragraph). Cantlay et al. teach that because GSTM4 has greater than 90% sequence homology with GSTM1, the polyclonal antibody could react with the product of both genes (see page 1011, 2nd paragraph). The intensity of the staining for some cells is at least 4 hold stronger than that for non-stained cells (see Figures 2(d) and (e)).

12. Claims 1, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Rowe et al. (Biochem. J. 1997, 325, 481-486).

Rowe et al. teach detection of GSTM4 polypeptide in lung tissues obtained from different subjects using antibody (see page 482, right column, 4th paragraph, Figure 1B and Table 1). Rowe et al. teach comparing the level of GSTM4 polypeptide between different subjects (see Table 1).

13. Claims 1, and 4-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Mol. Cell. Proteomics, 2002, April, 1:304-313).

Chen et al. teach detection of GSTM4 polypeptide in lung cancerous tissues and comparing the level of the GSTM4 polypeptide detected in cancerous tissue to that

detected in normal lung tissues (see page 306, Table). Chen et al. teach identifying the lung tumor stage (see page 310, and Table III).

Chen et al. do not specifically teach detecting the expression level of the TSTM4 polypeptide in lung cancer that is 4 fold higher than that in normal lung tissue. Because Chen et al. detected the same protein in the same type of lung cancer tissues, their detecting would encompass detecting the expression level of GSTM4 polypeptide that is 4 hold higher than that in normal lung tissue.

For this rejection, "prognosis" is interpreted as "the likelihood (or unlikelihood) of lung cancer subject's survival *as compared to* normal subject." Lung cancer patients inherently already have a smaller survival rate than normal subjects. Therefore, by teaching lung cancer detection, Chen et al. consequently teach prognosis.

14. Claims 1, 2 and 4-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Clin. Cancer Res., 2002, July 1st, 8: 2298-2305).

Chen et al. teach detection of GSTM4 polypeptide in lung cancerous tissues and comparing the level of the GSTM4 polypeptide detected in cancerous tissue to that detected in normal lung tissues (see abstract, and Table 1). Chen et al. teach that the expression of the GSTM4 polypeptide in lung cancerous tissue was 4 fold higher than that in normal lung tissue (see abstract and Table I). Chen et al. teach correlation of the expression level of the GSTM4 polypeptide to the tumor stage (see Table 2).

For this rejection, "prognosis" is interpreted as "the likelihood (or unlikelihood) of lung cancer subject's survival *as compared to* normal subject." Lung cancer patients

inherently already have a smaller survival rate than normal subjects. Therefore, by teaching lung cancer detection, Chen et al. consequently teach prognosis.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Hong Sang, Ph.D.
Art Unit 1643
May 4, 2007